



INFECTIONS IN SARCOIDOSIS

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ABSTRACT

Sarcoidosis is autoimmune disease known from century whose exact etiology is still under debate. Sarcoidosis is a chronic disease and numbers of infections have been reported in sarcoidosis patients. Some of the infections are more commonly reported while other are rarely reported in sarcoidosis. In this paper, we try to review opportunistic infections in sarcoidosis if there are any particular conditions which are more prone to the certain type of infections in sarcoidosis. The paper and research published online in the medical journal about infections in sarcoidosis were reviewed as early as possible. The risk for opportunistic infection in sarcoidosis is low and types of infections cause in sarcoidosis may depend upon epidemiology, therapeutic status, sarcoidosis stage, sarcoidosis site and CD+4 count.

Key words: Sarcoidosis, infection, corticosteroids, Immunosuppressive drugs, CD+4

INTRODUCTION

Sarcoidosis is a multisystem inflammatory disease which manifests as noncaseating granulomas, predominantly in the lungs and intrathoracic lymph nodes, but it can involve any part of the body more commonly peripheral parts of the body such as in the skin and eyes. Sarcoidosis in most of the patient is self-limited which resolves within two to five years but chronic form of the disease can cause significant morbidity and even mortality in some percentage of cases. More than one-third of sarcoidosis patients have chronic, unremitting inflammation with progressive organ impairment. However, the cause of exact pathology is still unclear. Death in sarcoidosis patient is less than 5% and it is the result of respiratory failure due to pulmonary fibrosis, or involvement of other important organs like cardiac or CNS and opportunistic infection. Prognosis depends upon the ethnic and genetic factors, organ involvement and initial presentation.

Opportunistic infections in sarcoidosis are rare and can cause moderate to fatal complications in sarcoidosis. Sarcoidosis itself is not the primary cause of infections in most of the case but cystic lungs or damaged pulmonary structure, immunosuppressive drugs used for the treatment for sarcoidosis, sarcoidosis site, epidemiology and condition like CD4+ T-Lymphocytopenia are the major cause of infections [1, 2]. Infections in sarcoidosis are opportunistic and usually complicate with fungal infections which are usually caused by deep seated fungal pathogens[1]. Other viral and bacterial infections are very rare[1, 2] . The opportunistic infections in sarcoidosis are from localized to invasive [1, 2]. Localized infection is mostly associated with lung parenchymal damage whereas invasive infection is associated with long-term steroid or immunosuppressive therapy and CD4+ T Lymphocytopenia[1, 3]. Intra-thoracic infections are more common and are mostly localized, and extra-thoracic infections are less common and mostly invasive[1].

Common Infections in sarcoidosis:

Aspergillosis:

Aspergillosis is the fungal infection caused by *Aspergillus* species. Aspergilli are ubiquitous mold which is normally found in surrounding environment and doesn't cause the disease in the healthy host. But, in the host with immune suppressed, damaged lung or in the allergic lung, it can cause opportunistic infection. *Aspergillus* mainly affects lung and cause infections like aspergilloma, invasive aspergillosis, chronic necrotizing aspergillosis and allergic bronchopulmonary aspergillosis. In sarcoidosis, the Aspergillosis infection is commonly non-invasive and chronic type. The underlying pathology and abnormal structure of lung due to sarcoidosis are the main reason for the development of chronic pulmonary Aspergillosis(CPA) type of infection[3, 4]. Sarcoidosis accounts for about 7-17% of total CPA infection[3], although sarcoidosis is not the major underlying cause of CPA. But, CPA is most common non-invasive and intra-thoracic infection in sarcoidosis[3]. CPA complicates 3-12% cases of sarcoidosis[3]. CPA commonly includes aspergilloma,

aspergillus nodule, chronic cavitary pulmonary Aspergillosis and chronic fibrosing pulmonary Aspergillosis. Aspergilloma is the most common aspergillosis infection in sarcoidosis patient[4]. Aspergillus fumigatus is the most common cause of aspergilloma[3]. Aspergilloma infection only reported in the advanced stage of sarcoidosis stage 4 or cystic stage[3, 6]. No case of aspergilloma has been described in non-cystic stage or in the early stage of sarcoidosis.[6] Studies have demonstrated that 11.3% of sarcoidosis patient develop aspergilloma and all sarcoidosis patients developed aspergilloma were in the advanced cystic stage or stage 4 [5] . In the year 1984 the paper published on aspergilloma complicating sarcoidosis documented that all aspergilloma developed in stage 3, but stage 3 in this paper was mentioned as most advanced and the last stage of sarcoidosis[6]. Few studies have suggested aspergilloma to be more common in a man with cystic stage than women, more common in those with a history of chronic smoking. Moreover, black race was more commonly affected than white race[6,7]. Corticosteroids and CD4 lymphocytopenia have no roles in aspergilloma formations or in CPA[6]. Hemoptysis is the common symptom documented in aspergilloma and Pulmonary hemorrhage due to aspergilloma is the 2nd leading cause of death in sarcoidosis patient after cardiorespiratory failure[7-9]. As to my knowledge one case of Allergic bronchopulmonary aspergillosis has been reported in sarcoidosis patient who was receiving infliximab, the author had explained drug infliximab play a role in developing allergic bronchopulmonary aspergillosis than sarcoidosis itself [8]. Few cases of invasive aspergillosis documented in sarcoidosis patient with prolonged neutropenia and immunosuppression[11, 12].

Cryptococcosis:

Cryptococcosis is life-threatening opportunistic fungal infection infections caused by encapsulated yeast in immune deficiency patients. Cryptococcosis infection most commonly occurs in HIV-infected patient and less commonly in immune suppressed patient such as reticuloendothelial malignancy, organ transplanted patients, sarcoidosis or patients under corticosteroid therapy. Cryptococcosis is one of the most common invasive infection reported in sarcoidosis patients[1] [10]. A retrospective study of Cryptococcosis infection done in France from 1985 to 2010, among 2749 cases, 18 cases of cryptococcosis reported complicating sarcoidosis and sarcoidosis accounted for 0.6% of all the cryptococcosis patients and about 2.9% of the cryptococcosis in non-HIV patients[11] . In 9 year of a survey on the epidemiology of cryptococcosis in France, corticosteroids therapy accounted for 33% of total cryptococcal infections in the non-HIV patient [12]. But in the case of cryptococcosis, some studies suggested that sarcoidosis is itself an independent factor for cryptococcal infection[10]. Cryptococcosis is a significant opportunistic infection during extrathoracic sarcoidosis and it's not associated with severe CD4 lymphocytopenia and steroid therapy[11] [10] [13] [14]. And steroid therapy and immunosuppressive drugs only help to facilitate the dissemination of the cryptococcal infection than having a direct role in causing cryptococcal infection[1]. However some studies bias, the use of the anti-TNF-alpha drug, which is reported of causing a significant number of cases of cryptococcosis infections in rheumatoid arthritis also reported to cause cryptococcal infection in

sarcoidosis[15]. However, some previous studies believed that immunosuppression and T cell abnormalities as the major factors for cryptococcal infections in sarcoidosis[13]. Extra-pulmonary sites such as central nervous system, bone, skin are the common sites for cryptococcal infection [1] [11]. A study by C. Bernard et al' demonstrated that among total cryptococcal infection in sarcoidosis, 72% had a CNS fungal involvement, 22% had skin or soft tissue, 17% had a bone or joint involvement, 11% had hepatic and 6% had a pulmonary cryptococcal infection and 22% had disseminated infection [11]. Cryptococcal meningitis should be suspected in sarcoidosis patient with any neurological abnormalities in sarcoidosis patients[14] [16] [17] . Cryptococcus neoformans is the most common organism causing cryptococcal infections in sarcoidosis [13][11] [16] [18]. Most cases of cryptococcosis infections reported in sarcoidosis are on stage II but the relevance of cryptococcal infections in stage II sarcoidosis is not explained yet[11].

Progressive multifocal leukoencephalopathy:

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by John Cunningham virus (JC virus). JC -virus-specific antibodies are normally detected in 80% healthy adult and infection remains latent in healthy individuals. But under conditions of severe immunosuppression, the virus activates and cause demyelination of CNS. 85% of PML cases have been reported in HIV patients, and about 15% of PML cases in other immunodeficiency diseases such as lympho or myeloproliferative disorders, autoimmune diseases, iatrogenic immunosuppression, chronic-inflammatory, granulomatous or infectious diseases. A retrospective study showed about 9% of PML to be associated with sarcoidosis in the non-HIV patient [19] [20]. The course of the disease is sub-acute and characterized by altered mental status, motor deficits, ataxia and impaired visual symptoms. PML patients T2 weighted MRI image show diffuse hyperintense lesion of the white matter of the brain, Blood reports show a shift in CD4/CD8 ratio, T-lymphocytopenia and increase the level of Angiotensin-converting enzyme (ACE), CSF PCR positive for JC-virus [20] [21] [22] [23]. The clinical presentations, MRI images, CSF PCR test for JC virus, immunocytochemistry and cerebellar biopsy used together to diagnose PML. Few case of PML have been reported in sarcoidosis, however, the cause of developing PML in sarcoidosis patient remains unclear. Some authors have suggested that the shift of CD4/CD8-ratio or secondary to T-lymphocytopenia resulting from an underlying sarcoidosis, increases the risk for developing PML [24]. Many sarcoidosis patients have been reported to develop PML who were not under corticosteroid therapy for sarcoidosis and in some case, sarcoidosis and PML diagnosed at once ⁶², [20] [24]. The studies suggested that the corticosteroids don't any have a role in developing the PML but administration of corticosteroid in PML patient can rapidly progress the course of disease [23] [25] . PML can be considered in sarcoidosis patient if have any neurological symptoms and corticosteroid treatment should be stopped to delay progression of PML [22]. The curative treatment of PML is not discovered yet and its prognosis is very poor[22] [21] [22] [20]. But the course of PML can be delayed by interrupting immunosuppression and improving host immunity using antiviral

therapy against JC-virus[23] [25] [26].

Mycobacteria:

Since early 90's Mycobacterium organisms are widely mentioned as an etiological agent for sarcoidosis[27] [28] [29] [30]. The presence of mycobacteria in sarcoidosis lesion in much higher proportions than control group suggest a strong association between mycobacteria and sarcoidosis[31] [29]. The review was done in 1996 by Zumla and James about mycobacteria's as cause of sarcoidosis, in 15 studies only three study shows negative results. some researchers even consider tuberculosis and sarcoidosis as different aspects of the same disease, however, others disagree[32]. Tuberculosis drugs tried for sarcoidosis treatment also have shown negative results. Therefore its relationship is still in debate. The cases of Mycobacterium tuberculosis and non-mycobacterium tuberculosis infections have been reported in sarcoidosis patient. And Mycobacterium tuberculosis was reported as one of the most common infection in sarcoidosis patient in early 90 century. But very few cases have reported in recently and some cases reported as the coexistence of pulmonary tuberculosis and sarcoidosis. Maybe immunizations, preventions, and treatment of tuberculosis are the major cause of the sudden decrease in the incidence of tuberculosis in sarcoidosis patient. The review was done by Yvan Jamilloux et al' presented total 27 known cases of sarcoidosis among whom 74% of patient were under corticosteroid and immunosuppressive treatment for sarcoidosis and 72% have extra-pulmonary features of sarcoidosis[4]. Opportunistic infections with nontuberculous mycobacteria in immunocompromised patients are usually insidious and severely disseminated , however, it is very uncommon in sarcoidosis [33] [34] [10] [4]. Two cases of fatal disseminated nontuberculous infections with Mycobacterium genavense have been reported in sarcoidosis patient who was in long term steroid therapy[35]. Total 14 cases of non-tuberculosis mycobacterial infections have been reported in patients with sarcoidosis among which 71% of patients were under corticosteroids or immunosuppressant therapy[4]. The author suggested Sarcoidosis associated immunosuppression is not a major risk factor for mycobacterial infection but epidemiological factors and immunosuppressive drugs are strong risks factors for mycobacterial super-infection[4].

Other opportunistic infections in sarcoidosis:

Total eight cases of histoplasmosis infection have been reported in sarcoidosis[4]. Endemic area and immunosuppressive drugs are reported as the major cause of opportunistic infections than sarcoidosis itself[1]. The case of pulmonary histoplasmosis reported which later develop sarcoidosis and role of histoplasmosis suggested for sarcoidosis etiology [36] . Due to similar Symptoms and radiological signs for both histoplasmosis and sarcoidosis, it can give diagnostic dilemma and wrong treatment even worse the clinical conditions [37]. Nine cases of herpes zoster infections have been reported in sarcoidosis and all patients have extra-thoracic involvement. All patients have a history of long-term corticosteroid therapy[4].

Pneumocystis Carinii is one of the most common opportunistic infection in AIDS patient and also has been reported in a person with idiopathic CD4+ T lymphocytopenia. two cases of pneumocystis carinii reported in sarcoidosis and both cases have Idiopathic CD4+ Lymphocytopenia[38]. Pulmonary nocardiosis has reported in sarcoidosis patients who were receiving corticosteroids and with CD4+ T-lymphocytopenia[39]. Two cases of invasive blastomycosis reported in sarcoidosis patients who was on immunosuppressive therapy for sarcoidosis treatment [1]. Three cases of leishmaniasis reported in sarcoidosis and all three case were in corticosteroids therapy, however, the author suggests an endemic area for such protozoa are major risk factors[40]. Leishmaniasis infections have the same manifestation as sarcoidosis and cutaneous leishmaniasis may be misinterpreted as sarcoidosis so, in endemic areas, any granulomatous skin disease compatible with sarcoid type granuloma should be further investigated. Two cases of Rhodococcus infections reported in sarcoidosis patient who was under corticosteroid treatment and history of visiting endemic area[41]. one case of Chronic mucocutaneous candidiasis reported in sarcoidosis patient. [42].

CONCLUSION

Tuberculosis, histoplasmosis, leishmaniasis, stronglyides, rhodococcus infections have been reported in sarcoidosis patient who had a history of visiting the related endemic area. Aspergilloma has been reported only in cystic lungs. PML, pneumocystis carinii, pulmonary nocardiosis, and chronic mucocutaneous candidiasis have reported in sarcoidosis patients who have low CD4 counts or T-Lymphocytopenia. Cryptococcus and herpes zoster infections are reported in extra-pulmonary sarcoidosis. Cryptococcus infections are independent of immunosuppressive therapy and CD4 lymphocytopenia. Immunosuppressive drugs and corticosteroids therapy for a long term increase the chances for invasive or disseminated infections in sarcoidosis. So on the basis of sarcoidosis site, stage, CD4 counts, therapy status and history of visiting the endemic area, the physician should be aware of the types of infections sarcoidosis patient are under risks and can take proper measure to diagnosis and prevent infections in sarcoidosis patients.

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